

# Noise-aided Logic in an Electronic Analog of Synthetic Genetic Networks

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## Abstract

We report the experimental verification of noise-enhanced logic behaviour in an electronic analog of a synthetic genetic network, composed of two repressors and two constructive promoters. We observe good agreement between circuit measurements and numerical prediction, with the circuit allowing for robust logic operations in an optimal window of noise. Namely, the input-output characteristics of a logic gate is reproduced faithfully under moderate noise, which is a manifestation of the phenomenon known as *Logical Stochastic Resonance*. Interestingly, the two dynamical variables in the system yield complementary logic behaviour simultaneously, indicating strong potential for parallel processing.

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## I. INTRODUCTION

Realization of logic functions in different physical systems is one of the key questions that commands widespread research interest in sciences and engineering. Universal general-purpose computing devices can be constructed entirely from NOR/NAND logic gates [1]. It is particularly interesting to investigate if systems of biological relevance can also yield logic outputs consistent with the truth tables of different logic functions (see Table I).

A new idea in this direction uses the interplay between noise and nonlinearity constructively to enhance the robustness of logic operations. Namely, in an optimal window of noise, the input-output characteristics of a logic gate is reproduced faithfully. This phenomenon is termed *Logical Stochastic Resonance* [2, 3].

In this work we investigate the possibility of obtaining such reliable logic outputs experimentally, in an electronic analog of a noisy biological system of considerable interest: a synthetic genetic network [4]. We demonstrate the *pivotal role of noise in the optimization of the logic performance in this circuit*. Further, we show the capacity for *parallel processing logic functions*, with complementary logic outputs obtained simultaneously [5].

Since understanding the intercellular processes in a network of interacting biomolecules is difficult, an alternative approach has been started recently [6], to design artificial genetic networks to derive desired functional behaviors. One important early design is a clock using three genes inhibiting each other in a cyclic order. Each gene produces a repressor to the subsequent gene. The genes each produce their own mRNA, which translate the repressor protein. Taking into account the standard chemical kinetics for production, degradation and inhibition, a dynamical system model was proposed [7] where the repressor-protein concentrations and mRNA concentrations were expressed as dynamical variables.

Here we use two such repressors and constructive promoters as our model system for implementing logic functions. First we describe the synthetic gene network model below, and define what constitutes logic inputs and logic outputs in this system. We then go on to present the electronic analog of the system followed by a comparison of numerical simulation and experimental measurement.

Input Set $(I_1, I_2)$	OR	AND	NOR	NAND
(0,0)	0	0	1	1
(0,1)/(1,0)	1	0	0	1
(1,1)	1	1	0	0

TABLE I: Relationship between the two inputs and the output of the fundamental OR, AND, NOR and NAND logic operations. Note that the four distinct possible input sets (0, 0), (0, 1), (1, 0) and (1, 1) reduce to three conditions as (0, 1) and (1, 0) are symmetric. Note that *any* logical circuit can be constructed by combining the NOR (or the NAND) gates [1].

## II. SYNTHETIC GENETIC NETWORK MODEL AND LOGIC OPERATION

We consider the model of two genes inhibiting each other. The concentrations of the two expressed proteins are  $x$  and  $y$ , and their rates of change are:

$$\frac{dx}{dt} = \frac{\alpha_1}{1 + y^n} - \beta_1 x + g_1 + D\eta(t) \quad (1)$$

$$\frac{dy}{dt} = \frac{\alpha_2}{1 + x^n} - \beta_2 y + g_2 + I_1 + I_2 + D\xi(t) \quad (2)$$

where  $\beta_1, \beta_2$  are the rate of decay of each expressed protein and  $n$  is the Hill coefficient. The  $\alpha_1, \alpha_2$  describe the maximum transcription rate in absence of inhibition and they are used here as tunable parameters. In the original model  $g_1$  and  $g_2$  represent leakiness of the promoter. However we use them as constant bias. The additive noise has strength  $D$  and  $\eta$  and  $\xi$  are chosen from unit variance zero mean Gaussian distributions.  $I_1$  and  $I_2$  are two *low amplitude* inputs.

The system above has two stable configurations in the  $x - y$  plane: one state has a high value of  $x$  ( $x_u$ ) and a low value of  $y$  ( $y_l$ ); the other state has a low value of  $x$  ( $x_l$ ) and a high value of  $y$  ( $y_u$ ). That is, the two dimensional potential underlying this system has two wells,  $(x_u, y_l)$  and  $(x_l, y_u)$ , in the  $x - y$  space. Varying the parameters changes the depth and position of these wells.

**Encoding Inputs:** Here the low amplitude input signal is  $I = I_1 + I_2$ , with  $I_1/I_2$  equal to  $I_{ON}$  ( $I_{ON} > 0$ ) if the logic input is 1, and  $I_1/I_2$  being 0 if the logic input is 0. So we have:

- (i)  $I_1 + I_2 = 0$  corresponds to logic input set (0, 0)
- (ii)  $I_1 + I_2 = I_{ON}$  corresponds to logic input sets (0, 1)/(1, 0)

(iii)  $I_1 + I_2 = 2I_{ON}$  corresponds to logic input set  $(1, 1)$

### Output :

The outputs of the system are determined by the level of the dynamical variables  $x(t)$  and  $y(t)$ . For instance the output can be considered a logical 1 if the state is at the high level, and logical 0 if it is at the lower level. That is:

- (i) If  $x < x^*$ , then Logic Output is 0
- (ii) If  $x > x^*$ , then Logic Output is 1

Here  $x^*$  is the *output determination threshold* that lies between the two states, e.g., at the position of the barrier between the wells. The results presented here are not sensitive to the specific value of  $x^*$ .

Specifically, in this work, we consider the logic output to be 1 when the state is close to the upper well, and 0 when the state is close to the lower well, for both  $x$  and  $y$  variables. So when the system switches wells, the output is “flipped” or “toggled”.

## III. CIRCUIT REALIZATION

The circuit of a single inhibitory gene [8] is shown in Fig. 1. The transistor current represents the rate of gene expression and the voltage  $V_{out}$  represents the concentration of expressed protein. The  $V_{cth}$  adjusts the binding constant of the repressor to the gene’s DNA. The Hill function inhibition in Eqs. 1-2 is accounted for by the dependence of the transistor current on input voltage  $V_{in}$  which represents the repressor concentration. The synthetic genetic network shown in Fig. 2 is comprised of two individual gene circuits connected in a loop, each inhibiting the other. For the model in Eqs. 1-2, the encoding inputs  $I_1$  and  $I_2$  add to production of  $y$  which is accounted for in Fig. 2 by the two logic driven transistors sourcing current to  $V_y$ .

The circuit equations are obtained by applying Kirchoff’s laws to  $V_x$  and  $V_y$ , the voltages across the capacitors in Fig. 2 as in Ref. [8]. Multiplying both equations by  $R_y$  results in

equations for  $V_x$  and  $V_y$ ;

$$R_y C \frac{dV_x}{dt} = -\frac{R_y}{R_x} V_x + \frac{R_y}{R_x} V_{x-noise} + R_y i_t \quad (3)$$

$$R_y C \frac{dV_y}{dt} = -V_y + V_{y-noise} + R_y i_t + R_y i_1 + R_y i_2 \quad (4)$$

where  $i_t$  is the transistor current in Fig. 1 for each gene, and  $i_1$  and  $i_2$  are the logic train transistor currents in Fig. 2. The variables  $(x, y)$  in Eqs. 1-2 are related to voltages  $V_x$  and  $V_y$  by:

$$x = \frac{V_x}{V_{th}}, y = \frac{V_y}{V_{th}}$$

where  $V_{th}$  corresponds to the repressor's equilibrium binding constant. The connections between model parameters  $(\alpha_i, \beta_i, n)$  and circuit parameters are found by relating circuit Eqs. 3-4 to the model Eqs. 1-2 and by adjusting the dependence of the transistor current  $i_t$  on  $V_{in}$  to match the Hill function inhibition (see *Appendix* for details).

A noise generation circuit shown in Fig. 3 based on breakdown of a reverse biased base-emitter junction produces noise with zero mean and variable amplitude. We use a well regulated supply for the noise circuit to avoid adding AC frequencies into the noise. Two of these noise circuits are used to supply noisy voltages to each individual gene at locations indicated in Fig. 2. The amplitude  $D$  of the gaussian noise in the model is related to the rms value of the noise voltage by  $D = V_{rms}/V_{th}$ .

#### IV. RESULTS AND DISCUSSION

Figure 4 shows measurements from the circuit using  $n = 2.4$ ,  $\alpha = 1.78$ ,  $\beta_1 = 0.90$ ,  $\beta_2 = 1$ ,  $I_{High} = 0.062$  for different strength of noise. It is apparent that for noise levels within an optimal range (Fig. 4c) the circuit indeed performs the logic AND/NAND function. These measurements agree well with the numerical simulations of Eqs. 1-2 shown in Fig. 5 using the Euler-Maruyama method with a step size of  $\Delta t = 0.025$ .

One can also *reconfigure* the system to another set of logic functions, namely the fundamental OR/NOR logic, by simply changing the value of  $g_2$ . For instance when  $g_2 = 0.06 - 0.07$  (with all other parameters unchanged), one gets a clear OR and the complementary NOR response from the system. Inclusion of  $g_2$  in the circuit is achieved by including a current sourcing transistor in the same way as the encoding signal transistors,

but with the logic train input being grounded. The same analysis as for the encoding values and currents (see *Appendix*) finds that  $g_2 = 0.062$ . Figures 6 and 7 demonstrate this capacity of reconfiguration in simulations and circuit experiments respectively.

In summary, our results show that the dynamics of the two variables  $x$  and  $y$  with  $g_2 = 0$ , mirror AND and the complementary NAND gate characteristics. Further, when  $g_2 \neq 0$ , we obtain a clearly defined OR/NOR gate. Since  $x$  is low when  $y$  is high and vice-versa, the dynamics of the two variables always yield *complementary* logical outputs, simultaneously. That is, if  $x(t)$  operates as NAND/NOR,  $y(t)$  will give AND/OR. This is significant, as it allows the system to yield two logic operations in parallel, thereby doubling the computational speed.

So our results here extend the scope and indicate the generality of the recently observed phenomena of Logical Stochastic Resonance (LSR) through experimental verifications. Further, these observations may provide an understanding of the information processing capacity of synthetic genetic networks, with noise aiding logic patterns. It also may have potential applications in the design of biologically inspired gates with added capacity of reconfigurability of logic operations and parallel processing.

Thus the results presented in this work suggest new directions in biomolecular computing, and indicate how robust computation may be occurring at the scale of regulatory and signalling pathways in individual cells and even within few biomolecules. Design and engineering of such biologically inspired computing systems not only present new paradigms of computation, but can also potentially enhance our ability to study and control biological systems [9].

### Acknowledgments

S.K.D. acknowledges support by the CSIR Network project "GENESIS".

### Appendix

We give a brief description of the analysis of the single gene circuit in Fig. 1, with more details in Ref. [8]. The op-amp U1 is configured as a subtraction amplifier with gain  $G_1 = \frac{11}{10} = 1.1$ . A replication of the Hill function behavior is achieved by allowing saturation

of the output of the op-amp U2 and by having different unsaturated gains  $G_{+2}$  and  $G_{-2}$  for  $V_{in} > V_{cth}$  and  $V_{in} < V_{cth}$ , respectively, due to the diodes in the feedback for U2.  $G_{-2}$  is the gain of U2 when its output goes negative, in which case the diodes are not conducting, and therefore  $G_{-2} = \frac{3.3}{1.0} = 3.3$ .  $G_{+2}$  is a diminishing gain when the output of U2 becomes increasingly positive causing the diodes to go into conduction. An increasing repressor concentration corresponds to  $V_{in}$  surpassing  $V_{cth}$  which causes the unsaturated output at U2 to change from a negative voltage of  $G_1 G_{-2}(V_{in} - V_{cth})$  to a positive voltage  $G_1 G_{+2}(V_{in} - V_{cth})$ . The increasing voltage at the output of U2 turns the transistor off ( $i_t \rightarrow 0$ ) which corresponds to inhibition of protein expression. Transistor current  $i_t$  is maximum when the output of U2 is at its lower saturation value of  $V_{-sat} = -3.5$  V (for the LF412 op-amp supplied by  $\pm 5$  V) causing about a 0.65 V drop across the  $220\Omega$  and therefore the maximum current  $i_{max} = 3$  mA.

A comparison of Eqs. 1-2 with Eqs. 3-4 yields [8]:  $\alpha_1 = \alpha_2 = \frac{i_{max}R}{V_{th}}$ ,  $\beta_1 = \frac{R_y}{R_x} = \frac{470}{520} = 0.90$ ,  $\beta_2 = 1$ . The voltage  $i_{max}R$  is  $(3 \text{ mA})(0.45 \text{ k}\Omega) = 1.35$  V, where  $0.45 \text{ k}\Omega$  comes from the  $R_y = 470\Omega$  being nearly in parallel with the resistance ( $10 \text{ k}\Omega$ ) at the input to the subtraction amplifier U1 for gene-x. The characteristic time here is  $R_y C = (470)(10^{-8}) = 4.7 \mu\text{s}$ , and  $\tau = \frac{t}{R_y C}$  is the dimensionless time.

The relation for Hill coefficient  $n$  is found by adjusting the dependence of  $i_t$  on  $V_{in}$  to match the slope of the Hill function  $1/(1 + x^n)$  at  $x = 1$  resulting in the relation [8]:

$$\frac{fV_{th}G_1G_{-2}}{f(5 - V_{-sat}) - 0.6} = \frac{-n}{4} \quad (5)$$

In Fig. 1 the voltage divider fraction  $f = 0.4/2.6 = 0.154$  and  $V_{-sat} = -3.5$  V. Using  $\alpha = i_{max}R/V_{th}$  in Eq. 5 yields the parameter relation  $n\alpha = 1.17G_1G_{-2}$ . To find the relation between  $V_{cth}$  and  $V_{th}$  we note that the Hill function equals 0.5 when  $x = 1$ . Therefore  $i_t$  must be half its maximum value when  $V_{in} = V_{th}$  which gives

$$\frac{i_t}{i_{max}} = \frac{f(5 - G_1G_{-2}(V_{th} - V_{cth})) - 0.55}{f(5 - V_{-sat}) - 0.6} = 0.5.$$

Solving gives  $V_{cth} \approx V_{th} + \frac{1}{G_1G_{-2}}$ . Here we use  $n = 2.4$  and  $\alpha = 1.78$  which gives:  $G_1G_{-2} = (2.4 \times 1.78)/1.17 = 3.65$ , satisfied by  $G_1 = 1.1$  and  $G_{-2} = 3.3$ ;  $V_{th} = 1.35/1.78 = 0.76$  V; and  $V_{cth} = 0.76 + 1/3.65 = 1.03$  V.

The encoding signals  $I_1, I_2$  in Eqs. 1-2 are related to transistor currents by:

$$I_{1,2} = \frac{R_y i_{1,2}}{V_{th}}.$$

The encoding currents  $i_{1,2}$  in the transistors in Fig. 2 take on two possible values depending on whether their logic train input is high or low. When the input is high ( $> 4V$ ) the transistor is off so the current is zero. When the input is zero, there is 1V across the  $R_I = 10\text{ k}\Omega$  connected to the emitter of each *pnp* transistor creating current  $i_{1,2} = (1\text{ V})/R_I$ . Therefore the high level for each encoding input is  $(I_{1,2})_{High} = (R_y \times 1V)/(R_I V_{th})$ , e.g. for  $\alpha = 1.78$  then  $V_{th} = 0.76\text{ V}$  and the high level is  $470/(10k \times 0.76) = 0.062$ .

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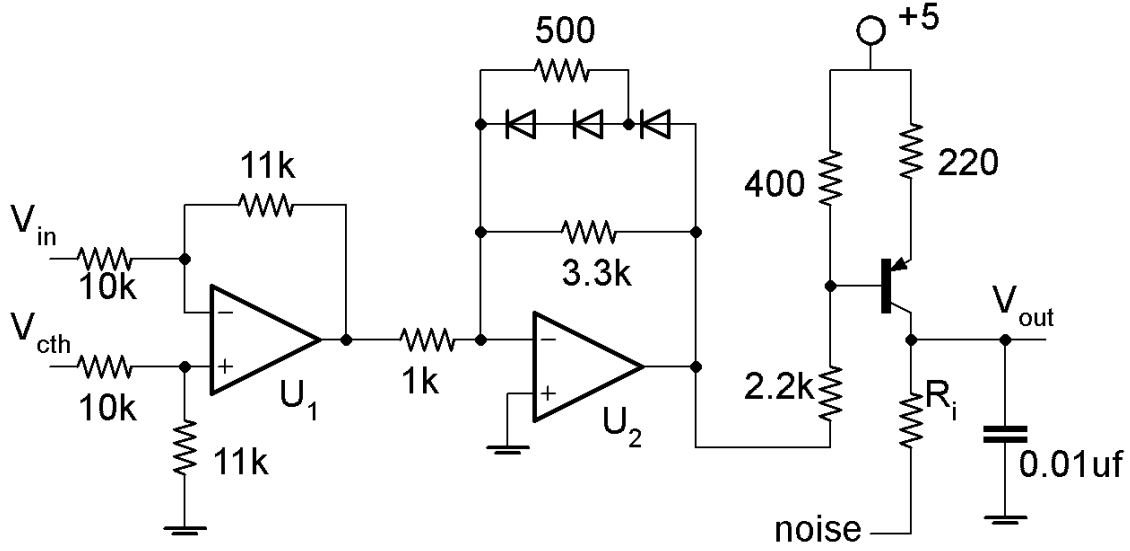


FIG. 1: Circuit for single gene. Inhibitory input at  $V_{in}$ . Expressed protein concentration is represented by  $V_{out}$ .  $R_i = 470 \, \Omega$  for gene- $y$ ,  $520 \, \Omega$  for gene- $x$ . Dual op-amp is LF412 supplied by  $\pm 5$  V. The *pnp* transistor is 2N3906. The input noise has a mean of 0 V (gnd) and controllable standard deviation.

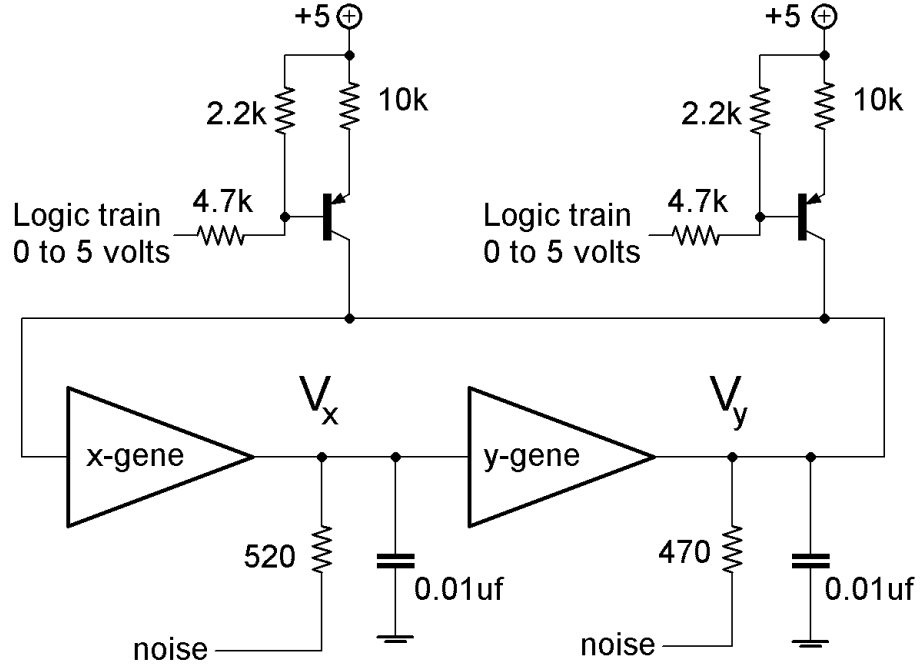


FIG. 2: Circuit for synthetic genetic network. Encoding inputs are 0 to 5 V pulse trains. The  $x$  and  $y$  gene circuits are shown in Fig. 1. Each noise input has its own noise circuit shown in Fig. 3.

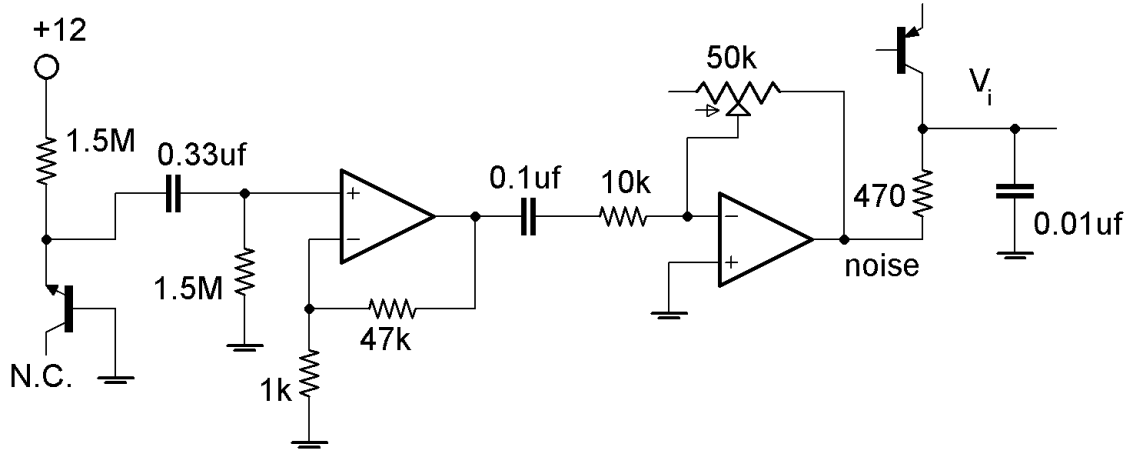
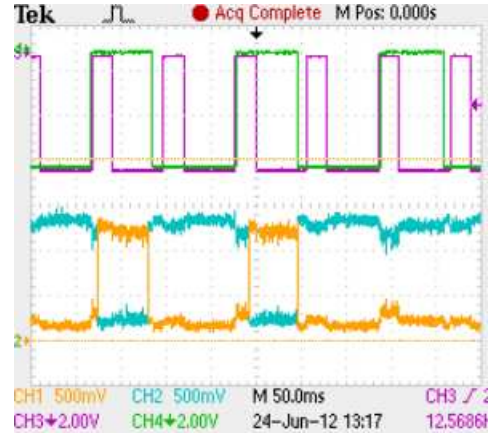


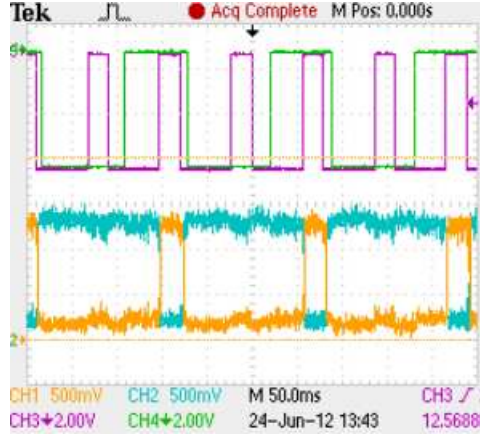
FIG. 3: Noise circuit and its connection to resistor of gene circuit. LF412 dual op-amps supplied from  $\pm 12$  V regulators.



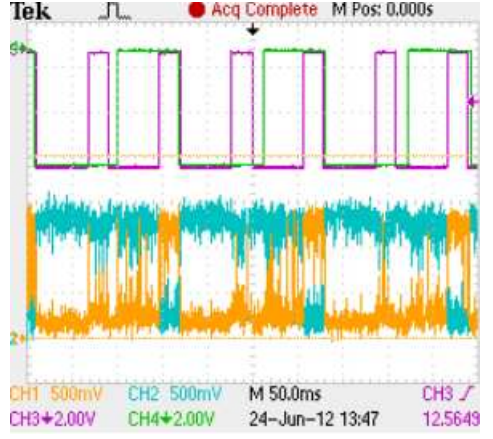
(a) 1.8 mV noise,  $D = 0.0024$ .



(b) 35 mV noise,  $D = 0.046$ .

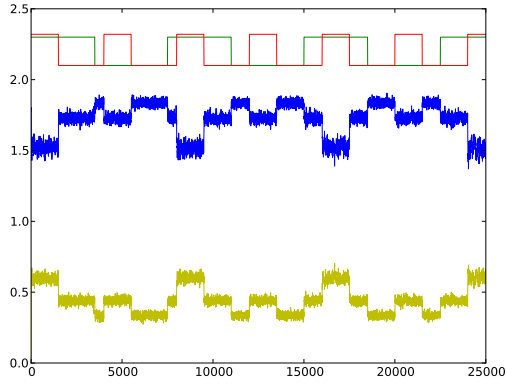


(c) 60 mV noise,  $D = 0.079$ .

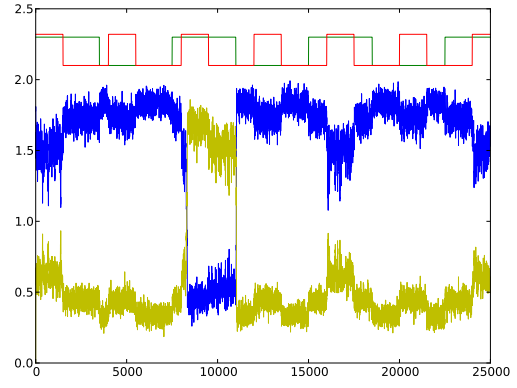


(d) 110 mV noise,  $D = 0.145$ .

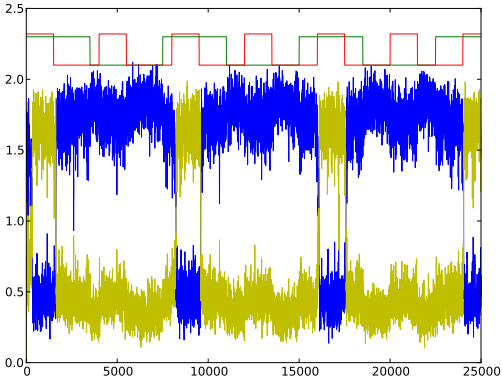
FIG. 4: Experimental measurements from circuit (cf. Eqs. 3-4) with different noise amplitudes.



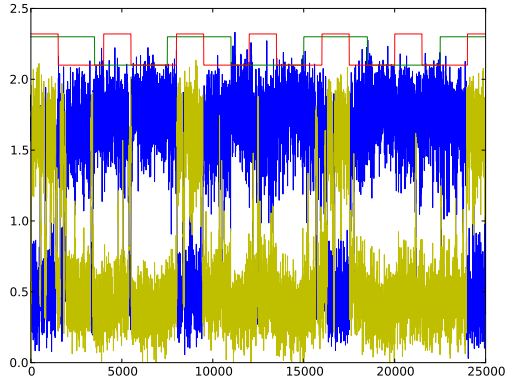
(a)  $D = 0.02$ .



(b)  $D = 0.05$ .



(c)  $D = 0.10$ .



(d)  $D = 0.16$ .

FIG. 5: Simulations of Eqns. 1-2, with different noise amplitudes.

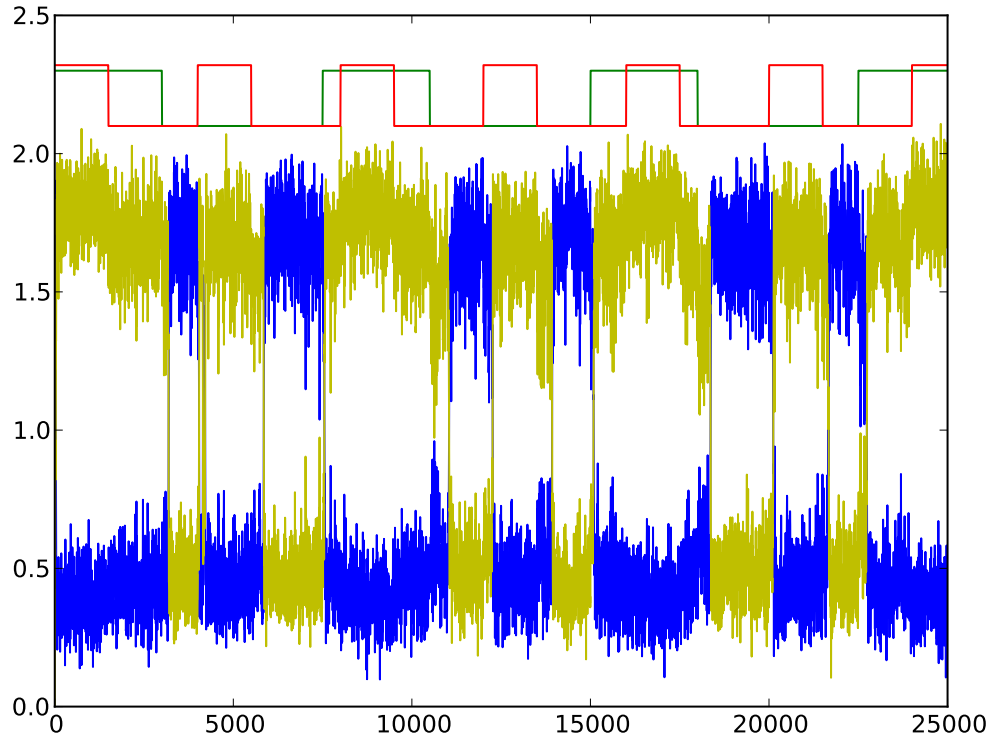


FIG. 6: Simulation of Eqns. 1-2 with  $g_2 = 0.07$  showing OR/NOR logic response. Here noise level is  $D = 0.11$ .

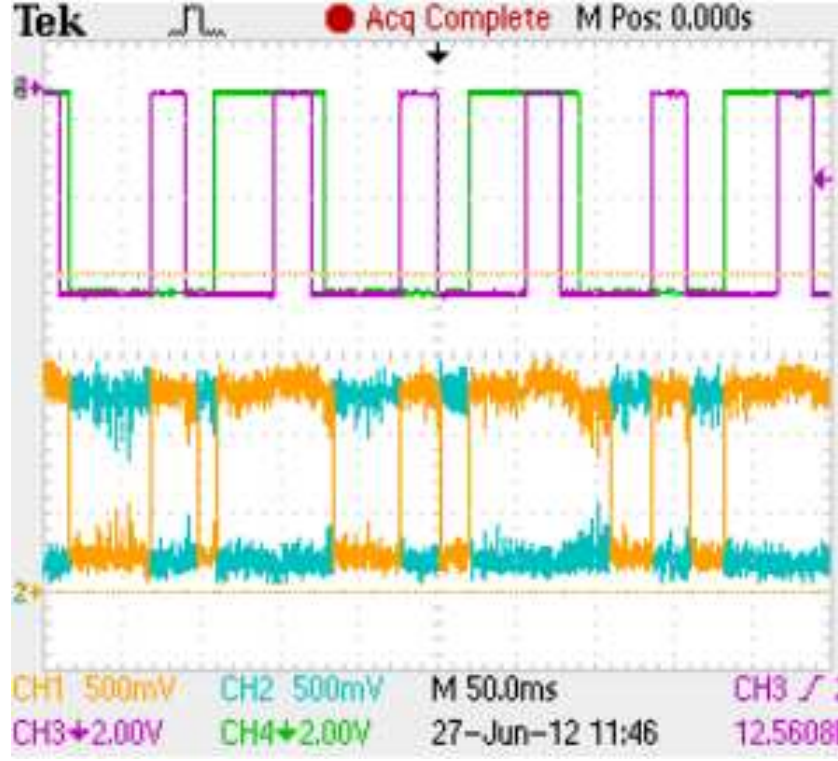


FIG. 7: Experimental measurements from circuit with  $g_2 = 0.062$  displaying OR/NOR characteristics (cf. Eqs. 3-4). Here noise level is  $D = 0.10$  (i.e. 75 mV rms).